

REMARKS

I. Status of Claims

Claims 1, 2, and 11-21 are pending in the application. Claims 3-10 were previously cancelled, and claims 2 and 11-21 were previously withdrawn.

II. Claim Rejections - 35 U.S.C. 112

Applicant respectfully thanks the Examiner for withdrawing the rejections under 32 U.S.C. 112, first paragraph as failing to comply with the written description requirement, and under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

III. Claim Rejections - 35 U.S.C. 103

On page 3 of the Office Action, the Examiner rejected claim 1 as unpatentable over WO 9726018 ("Pomerantz") in view of *Intramitochondrial Dyes Allow Selective In Vitro Photolysis of Carcinoma Cells*, PNAS, December 15, 1986, vol. 83, no. 24, 9729-9733 ("Oseroff") and *Supravital Staining of Mitochondria with Phenosafranin Dyes*, Biochem and Biophysics, 1953, pages 11480-11486 ("Brenner").

Applicant respectfully disagrees. Applicant submits that the Examiner has not met her burden in establishing a *prima facie* case of obviousness. The claimed invention is not obvious over the cited references.

The Examiner has cited Oseroff for its alleged disclosure of a genus of compounds and has stated that all of the claimed species are obvious based upon this disclosure. However, to support a *prima facie* case of obviousness, M.P.E.P. § 2144.08 recites: "when a single prior art reference which discloses a genus encompassing the claimed species or subgenus but does not expressly disclose the particular species or subgenus, Office Personnel should attempt to find additional prior art to show that the claimed invention as a whole would have been obvious. Where such additional prior art is not found, Office Personnel should consider the factors discussed below to determine whether a single reference 35 U.S.C. § 103 rejection would be appropriate."

Here, Applicant submits that the Examiner has not met her burden in establishing the *prima facie* case of obviousness. The Examiner has cited Oseroff for its alleged disclosure that "mitochondria preferentially accumulate and retain certain cationic dyes to a much greater extent than

most normal cells" and that "the reference [Oseroff] indicated that it is possible that other cationic molecules that concentrate within the mitochondria at higher levels or that is more efficient photosensitizers will still be more effective. Thus Oseroff invited people having ordinary skill in the art to try other cationic cyanine dyes in this respect and since the rejection is under 35 U.S.C. § 103, an invitation to try is correct to reject the genus" (Office Action, pages 4 and 6). Oseroff, as Examiner herself has conceded, does not expressly disclose the claimed species. Thus, Examiner should have attempted to find additional prior art to show that the invention as a whole would have been obvious. However, the only prior art that the Examiner has cited is Pomerantz and Brenner. Pomerantz discloses toluidine blue O, which is not claimed in the present invention. Brenner discloses one claimed dye, phenosafranin; however, as stated in the previous response to Office Action, Brenner discloses that the phenosafranin dye **does not** stain the mitochondria, contrary to what is claimed (i.e., page 485 of Brenner recites that " . . . In such preparations, Janus green B potentially inhibits oxidative phosphorylation, but this property is not shared by phenosafranin and other dyes which are not supravital mitochondrial stains . . . ". As such, Applicant submits that the Examiner has not found additional prior

art that shows that the claimed invention as a whole would have been obvious.

Since no additional prior art was cited, the Examiner should have established a *prima facie* case of unpatentability by considering the factors set out by the Supreme Court in *Graham v. John Deere*. Specifically, the Examiner should have: (a) determined the scope and content of the prior art; (b) ascertained the differences between the prior art and the claims in issue; (c) determined the level of ordinary skill in the pertinent art; and (d) evaluated any evidence of secondary considerations. Applicant submits that since the Examiner did not do so, she has not met her burden of establishing the *prima facie* case of obviousness.

Even if the Examiner did review the foregoing factors, the claimed invention is not obvious because neither Pomerantz nor Oseroff teach or suggest the dyes claimed as discussed above, as well as the claim element "the retention of said agent by the mitochondria of cancer cells in vivo which have been marked by absorption of said agent in the mitochondria thereof." On page 6 of the Office Action, the Examiner has alleged that "Oseroff also disclosed experimenting [with] the dyes in vivo (see page

9730 forth paragraph) . . . " Upon review of this paragraph, however, it discloses photolysis experiments done with EJ bladder carcinoma cells, which, as one skilled in the art knows, are in vitro experiments, as the title of Oseroff itself is the following: "Intramitochondrial dyes allow selective in vitro photolysis of carcinoma cells"

Additionally, M.P.E.P. § 2144.08 further recites: "The fact that a claimed genus or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness" However, contrary to M.P.E.P. § 2144.08, the Examiner appears to believe that the alleged disclosure of the genus is indeed sufficient to reject the species, as the Examiner has alleged: "Thus, Oseroff invited people having ordinary skill in the art to try other cationic dyes in this respect and since the rejection is under 35 U.S.C. 103, an invitation to try is correct to reject the genus" (Office Action, page 4). So it appears that the Examiner is simply stating that review of Oseroff will make one of ordinary skill in the art to try other cationic dyes. A print out from Sigma-Aldrich's website lists over 1,000 staining dyes. See attached Exhibit A. Basically, Examiner is stating that given Oseroff, it would be obvious to try the dyes claimed (from an entire genus of over 1,000) to come up with the claimed

invention. It follows that the Examiner is of the opinion that it would be obvious to try the claimed dyes from the language "cationic dyes" in Oseroff, a group that could includes upwards of 1,000 dyes, to come up with the claimed invention. The sheer number of dyes itself is evidence of the unpredictable nature of the specific dyes claimed; namely, one would have to experiment with a large number of dyes to come up with the dyes claimed.

In addition, in a recent post-KSR Federal Circuit decision, *Sanofi-Synthelabo v. Apotex Inc.* (89 USPQ2d 1370), the Court affirmed the district court holding that a claim of a patent which recites a dextrorotary enantiomer of a specific compound substantially separated from its levorotary enantiomer is not invalid for obviousness over prior art references that disclose "racemate PCR 4099," from which dextrorotary enantiomer may be separated, since one skilled in the art would not have reasonably predicted from the reference disclosure that dextrorotary enantiomer would provide desired antiplatelet activity. Additionally, the Court found that disclosure of a genus in the prior art is not necessarily disclosure of every species within its scope, since "[prior art] references state generally that racemate compounds consist of enantiomers, but nothing in reference disclosure would have led [a] person of ordinary

skill in the art to recognize either explicit or inherent disclosure of racemate's dextrotary enantiomer or its bisulfate salt . . . "

Here, Examiner has alleged that " . . . since Oseroff teaches the generic concept of using cationic dyes, it is possible that other cationic molecules that concentrate within the mitochondria would be obvious to one skilled in the art as well . . . " However, Applicant submits that each of the specific dyes claimed in the present application are not obvious in view of the cited references. The specific dyes claimed, akin to the salt and dextrorotary enantiomer in Apotex, are not obvious upon review of the cited reference [Oseroff] which Examiner has alleged discloses "cationic dyes" (akin to the racemate mixture disclosed in the prior art in Apotex). One of ordinary skill in the art could not have predicted all that all of the dyes claimed would stain the mitochondria in vivo as presently claimed.

With respect to Brenner, the Examiner recites in the Office Action: " . . . phenosafranin was disclosed generically in the instant specification once . . . thus the janus green B (diethylsafranin is a species derived from the genus phenosafranin taught by the instant application) is a species which reads on the generic

disclosure . . . " Applicant submits, as discussed in the previous Office Action response, that "to test this hypothesis, a series of symmetrical and unsymmetrical phenosafranin dyes were investigated for their supravital staining activity." The results of the investigation in Brenner are outlined in Table II on page 482. Table II of Brenner shows that phenosafranin does not stain mitochondria, contrary to what is claimed. As such, it would not be obvious to try the claimed invention upon review of Brenner.

However, should the application be in condition for allowance if phenosafranin is deleted from the claim, Applicant will delete phenosafranin from the claim in order to expedite prosecution and not for reasons of patentability.

Accordingly, since Examiner has not met her burden of establishing the *prima facie* case of obviousness, withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

CONCLUSION

In view of the foregoing, it is believed that all claims now pending patentably define the subject invention over the prior art of record and are in condition for allowance and such action is earnestly solicited at the earliest possible date.

Please charge our Deposit Account No. 10-0440 if any fees are necessary for this matter.

Respectfully submitted,
JEFFER, MANGELS, BUTLER &
MARMARO LLP

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By: Manali V. Dighe, Esq.
Reg. No. 56,856
1900 Avenue of the Stars
Seventh Floor
Los Angeles, CA 90067-4308
(310) 203-8080
CUSTOMER NO. 24,574